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EXAMINER

LIU, SAMUEL W

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/838,044

Applicant(s)

KASER ET AL.

Examiner

Samuel W Liu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 4 June 20002 .
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 1-14, 17-18 and 20-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 15,16 and 19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_ .
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_ .

### **DTAILED ACTION**

Applicants' amendment filed 4 June 2002 has been entered.

#### ***Election/Restrictions***

Applicant's election with traverse of Group VII, Claims 15-19, filed on 4 June 2002 (Paper NO. 5) is acknowledged. In view of Applicants' election, Claims 1-14, 17-18 and 20-39 are withdrawn from consideration as directed to non-elected invention (for the reason, see the following statement). Therefore, Claims 15, 16 and 19 are pending and examined in this Office Action.

Invention VII, Claims 15-19, are directed to a product, i.e. purified protein. Invention VIII (Claims 20 and 21) and invention X (Claim 23) are process of screening a library and purification of a ligand from a sample, respectively. Applicants argue that inventions VII, VIII and X should be examined together. Applicants' argument is unpersuasive as to the reasons stated below. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the purified protein can be used in a materially different processes, generating a proteinchip array to investigate signal transduction pathway or identify disease states, for example. In addition, the process of invention VIII, screening a library of molecule, and process of invention X, purification of a ligand from a sample, can be practiced using structurally different proteins or peptides. Therefore, invention VII is patentably distinct from invention VIII and X.

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Furthermore, invention VII and X are also directed to different and/or distinct methods, one is screening a molecular library, whereas the other is purification of ligand for the claimed protein. These methods differ with respect to methodologies, starting material, objectives, technical considerations, ingredients, endpoint or/and treatment outcome; therefore, each method is patentably distinct.

During a telephone conversation with David Streeter on 29 July 2002 an additional election was made with traverse to prosecute polypeptide SEQ ID NO: 6 of Group VII (Claims 15-19). Claims 17 and 18 (SEQ ID NO:7 and 8, respectively) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions. Claims 15, 16 and 19 are therefore pending and examined.

### ***IDS***

Applicant's Information Disclosure Statement, filed 30 August 1999 (Paper No:2 of the parental case SN: 09386493), is acknowledged. However, after reviewing the parental application, the following the references on the IDS list are not found: document NO: 1, 4, 5 and 9. Applicant is invited to submit such documents.

### ***Objection to Specification***

The disclosure is objected to because of the following informalities:

In page 2, line 23, the term "CYP1A1" needs to be spelled out fully for the first time; see also, page 2, line 26, "BPDE; and page 3, line 22, "PNAs".

Correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 16 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant application is directed to a polypeptides SEQ ID NO:6 and its use in diagnosis, prognosis and prevention of human disorder such as cancer and its complication caused by polycyclic aromatic hydrocarbon (PAH) compound (see page 1, lines 7-10 and lines 21-33). Benzo(a)pyrene (BP), a type of PAH compound, can cause cancer in laboratory animals (see page 1, line 21-22).

The instant application claims an oligopeptide comprising at least 6 sequentially amino acids of SEQ ID NO:6. The claim as written encompasses a broad genus of the variant peptide and immunogenic fragments (see below).

An adequate written description of the invention may be shown by disclosure of sufficient, relevant, identifying characteristics (i.e. structure and chemical/physical properties) so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Because the instant application includes a large quantity of variations (species of the genus), a requirement for sufficient description of variety of the variants, i.e. species, must be met in order to reflect that variation. The specification of the current application does not contain any actual reduction to practice of each individual molecule or/and fusion product of the invention.

The instant application has provided a description of isolation and identification of the polynucleotide encoding SEQ ID NO:6 protein and description of the sequence of the purified proteins encoded thereby. The instant application, however, insufficiently describes the biological role and therapeutic role of this protein or its significance. The instant specification sets forth that an antagonist (page 17, the second paragraph), an agonist of the protein may be administered to a subject to treat or prevent a disease which may be induced through exposure to PHA compounds (page 17, the four paragraph). All the above-motioned therapeutic uses are directed to protein sequence (PSEQ). PSEQ embraces exceptionally-divergent proteins SEQ ID NOs: 6, 7 and 8 which are distinct in their primary structure (e.g. 587, 218 and 83 amino acid residues, respectively), their posttranslational modification ( e.g. N-glycosylation, and phosphorylation modification, see page 8, last paragraph), and their interactions with cell signaling pathways (e.g. tyrosine kinase etc., see page 8, the last paragraph, and page 9, paragraphs 1-3). Thus, uses of the claimed SEQ ID NO:6 protein is not specifically disclosed and described by the specification.

The human polynucleotide SEQ ID NO: 1 encodes the disclosed protein SEQ ID NO:6. The specification provides an expression profile (indicating the presence of the nucleic acid molecule) of the polynucleotide SEQ ID NO:1 in response to exposure to BP-compound in various tissues, e.g. reproductive tissue, nervous tissue and gastrointestinal tissue (see Table 1). Yet, this does not necessarily reflect that the expressed protein level of SEQ ID NO:1 will be directly proportional to the extent of the exposure to BP-compound evidenced as the followings:

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(1) none of the expression profiles particularly represented are compared to BP-untreated tissue; (2) BP-treatment mediates multiple expressions of distinct and/or different mRNA species (see Table 1); as shown in Table 1, the result of the exposure to the pollutant compound BP induces the most abundant (67%) of SEQ ID NO:4 polynucleotide that encodes protein SEQ ID NO: 7 (218 amino acid residues which is structurally distinct from SEQ ID NO:6 protein that is the subject matter of the current application); and (3) Furthermore, polynucleotide expression (e.g. mRNA expression) does not necessarily manifests cellular level of matured protein i.e. posttranslationally modified protein in a direct and proportional manner (note that the current application is directed to the posttranslationally modified protein, see pages 8-9) absent factual indicia to the contrary.

Applicants sets forth a substantially purified protein (see Claim 15). However, Applicants provide no factual evidence with respect to the substantially purified protein (SEQ ID NO:6) and the purified protein mediated or the purified protein directed uses in therapeutics and diagnosis. Applicants predict the functional uses of the claimed protein based on inspection of the presence of the polynucleotide that encodes the interest protein in response to exposure to the PHA compound.

In view of the reasons as stated in the foregoing, applicants are not in the possession of (i) the substantially purified protein of SEQ ID NO:6; (ii) any oligo-fragments comprising at least 6 sequential amino acids of the SEQ ID NO:6; and (iii) any purified polypeptide encompassing any portion of SEQ ID NO:6 protein.

The current application sets forth an immunogenic fragment of the protein (see Claim 15). However, the claimed immunogenic fragment is not supported by a specific asserted utility

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because no particular amino acid sequence is claimed or asserted in the specification (note that any peptide fragments ( $\geq 5$  amino acid residues) are qualified for being used as the immunogenic fragments). Thus, applicants are not in the possession of any immunogenic fragments derived from SEQ ID NO:6.

The instant application claims an oligopeptide ( $\geq 6$  amino acid residues) and an immunogenic fragment thereof derived from the disclosed protein sequence (see Claim 15). In consideration of a polypeptide or polypeptide (genus) having at least 6 consecutive amino acid residue of SEQ ID NO:6 (587 amino acid residues), it is calculated that there are at least  $1.7 \times 10^5$  species of peptide fragments (species) different in length. There is, therefore, a large volume of the variants of peptide fragments. The specification of the instant application sets forth the oligopeptide or the portion of the SEQ ID NO:6 is useful for screening molecular libraries (e.g. peptide libraries, polyclonal libraries etc.). Because the fragments are highly variant, use of these fragments to screening a library of molecules or compounds would be highly unpredictable.

The above mentioned variations is further magnified by the following factors which are set forth by the current specification.

(1) Number and types of posttranslational modifications (see page 8, the last paragraph).

(2) Types of the pharmacologically binding molecules, e.g. agonist or antagonist (see page 17, the second and the fourth paragraph), which interact with the variant molecules, e.g. peptides (note that there is unpredictable number of ligands that would cross-react with the target peptides or proteins).

(3) Chemical labeling that is prerequisite for screening molecular libraries (see page 23, the second paragraph). Note that chemical labeling is a process of the covalent modification of subject

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(e.g. peptide or protein); thus, the chemical prosperities of labeled peptides or proteins would add the other unpredictable factor into the variant molecules as claimed (see the foregoing statement).

It is evident from the foregoing statement that the outcome of the use of the oligopeptides or the portions of protein is based on unpredictably enormous variants and would require undue experimentation and necessary guidance. Therefore, applicant is not possession of the claimed any peptide or polypeptide fragments derived from SEQ ID NO:6 and use of them therefore for screening molecular libraries produced by exposure to PAH toxic compound(s). An adequate written description requirement for the claimed oligopeptide or polypeptide fragments (portions of SEQ ID NO:6 protein) is not satisfied in the present application because the specification' disclosure does not render invention being reduced to practice through providing a sufficient description of a representative number of the variants.

Description of invention's reduction to practice, unaccompanied by any meaningful, distinguishing characteristics of evolved the peptide variants, is insufficient to satisfy written description requirement of 35 U.S.C. §112, since inventors could have provided description of claimed oligopeptide or portion of SEQ ID NO:6 protein, since actual reduction to practice may demonstrate possession of embodiment of invention, but it does not necessarily describe what invention is, and since, in context of present case, disclosure of manner in which invention was reduced to practice does not satisfy more fundamental written description requirement set forth in Section 112.

Claims 15, 16 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for construction of benzo(a)pyrene (BP)-treated rat liver

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cDNA library (see pages 18-19) and isolation of the cDNA clones (see pages 19-20), expression analysis using electronic subtraction to create a transcript image profile (see bridging pages 20-21), labeling the isolated polynucleotide for hybridization analysis (see bridging pages 21-22), production of specific antibodies against the peptide fragments deduced from isolated polynucleotide sequences, and screening for a molecular library using labeled isolated-polynucleotides (see pages 9-10 and 23), the specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, which is directed to a purified polypeptide that can be useful as a pharmaceutical composition formulated with a pharmaceutically acceptable carrier in order to evaluating and identifying the environmental pollutants and the pollutant-mediated disease or disorder states. However, the specification does not provide working example, teaching, direction or guidance as to chromatographic purification of the protein as claimed and use of the purified protein as a pharmaceutical composition via formulating with a pharmaceutically acceptable carrier in order to develop diagnostic and therapeutic agent for human condition, disease and disorders (see especially page 1, line 17-20, page2, lines 29-32 and page 4, lines 22-25).

The specification of the instant application only sets forth a pollutant compound benzo(a)pyrene (**BP**)-induced polynucleotides SEQ ID NO: 1 for the encoded polypeptides SEQ ID NO: 6 (see table 1, Figure 1A, Figure 2A and Figure 3). The specification is silent as to purification of the claimed polypeptides and the pharmaceutical composition comprising the polypeptide(s). Adequate written description requires more than a mere statement that it is part

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of invention. The specification disclosure of the current application is insufficient to enable skilled artisan to practice the invention as broadly claimed without undue experimentation.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention/The scope of the claims:

Claim 15 sets forth a substantially purified protein which is expressed in response to exposure to cellularly toxic BP, and the claimed also sets forth an oligopeptide (at least 6 amino acid residues) and an immunogenic fragment thereof derived from the disclosed protein sequence. However, Applicants provide no factual evidence with respect to the substantially purified protein (SEQ ID NO:6) and the purified protein-mediated or the purified protein-directed uses in therapeutics and diagnosis. Applicants predict the functional uses of the claimed protein based on inspection of the presence of the polynucleotide that encodes the interest protein in response to exposure to the PHA compound.

Since the protein (SEQ ID NO:6 recited in Claims 15 and 16) is a product of induction of adult rat liver which exposed to the pollutant compound BP, one of skilled in the art would not have known any variants (any oligopeptide or polypeptide fragments  $\geq 6$  amino acid residues and their capability of being useful for screening a library of molecules or compounds (see page 13, lines 23-27 and 31-32), e.g. polyclonal antibody library).

The instant application claims an oligopeptide ( $\geq 6$  amino acid residues) and an immunogenic fragment thereof derived from the disclosed protein sequence (see Claim 15). In consideration of a polypeptide or polypeptide (genus) having at least 6 consecutive amino acid residue of SEQ ID NO:6 (587 amino acid residues), it is calculated that there are at least  $1.7 \times 10^5$  species of peptide fragments (species) different in length. There is, therefore, a large volume of the variants of peptide fragments. The specification of the instant application sets forth the oligopeptide or the portion of the SEQ ID NO:6 is useful for screening molecular libraries (e.g. peptide libraries, polyclonal libraries etc.). Because the fragments are highly variant, use of these fragments to screening a library of molecules or compounds would be highly unpredictable.

The above mentioned variations is further magnified by the following factors which are set forth by the current specification.

- (1) Number and types of posttranslational modifications (see page 8, the last paragraph).
- (2) Types of the pharmacologically binding molecules, e.g. agonist or antagonist (see page 17, the second and the fourth paragraph), which interact with the variant molecules, e.g. peptides (note that there is unpredictable number of ligands that would cross-react with the target peptides or proteins).
- (3) Chemical labeling that is prerequisite for screening molecular libraries (see page 23, the

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second paragraph). Note that chemical labeling is a process of the covalent modification of subject (e.g. peptide or protein); thus, the chemical prosperities of labeled peptides or proteins would add the other unpredictable factor into the variant molecules as claimed (see the foregoing statement).

In view of the above statement, there are a large volume of the variants of peptides and proteins. Because the fragments are highly variant, use of these fragments to screening a library of molecules or compounds would be unpredictable as to expected outcome.

On the other aspect, applicants are not in possession of any immunogenic fragments of polypeptide of SEQ ID NO:6, since the specification provides no teachings, direction and working examples in regard to preparation of any fragments and testing for their immunogenicity.

The instant claim language includes subsequences (see Claim 15 (b) and (c)) in claim 15 and recites at least 6 consecutive amino acids of SEQ ID NO:6. Such a recitation does not require that the corresponding polypeptide possesses the full length sequence set forth in SEQ ID NO:6; but rather encompasses any subsequences or have per se been. However, the specification does not provide sufficient guidance as to which subsequences of SEQ ID NO:6 would be purified, labeled and utilized to screen a chemical library (e.g. [synthetic] peptide library) and/or a biological library (e.g. polyclonal antibody library). Neither the specification provides any working examples of any subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:6 would be selected for labeling in order to screen a library of molecules (e.g. DNAs, peptides, and antibodies etc., see page 13, lines 23-28) and for raising antibodies for diagnostic assay, and to establish which subsequence would be used to formulate the peptide subsequence with a pharmaceutical carrier in order for

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developing a pharmaceutical composition applicable for diagnosis, prognosis, prevention, and treatment of the pollutant-mediated diseases and complications (see page 13, lines 21-22).

(2) The state of the prior art:

The general knowledge and level of one skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The number of peptide or protein variants as claimed is large. Immunogenic fragments and pharmaceutical compositions of the peptides/proteins are highly variant. Each variant has different/distinct structure, one skilled in the art would have been required to perform undue experimentation to screen and characterize each peptide or protein variants for immunogenicity, pharmaceutical efficacy, and diagnosis in the treatment and/or prevention of disorders associated with exposure to toxic compound BP and other pollutants.

The specification of the current application sets forth a protein (SEQ ID NO:6) that possesses a folding structure in biochemical solution. Folded proteins structurally and immunogenically differ from the unfolded oligopeptide. Characteristics of the surface of a folded protein play an important role in antibody recognition. The amino acids may be widely separated in the linear structure of the protein but are close together when folded. The epitope recognition by an antibody are of two basic type 1) linear epitope that represent linear sequence of amino acids within oligopeptide or polypeptide, and 2) conformational epitopes in which the area recognized in the protein exists as a result of the 3-dimensional structure (i.e. folding structure) of the protein (see Miller, E. J. et al. *Am. J. Physiol.* (1991) 260, 1-12). Folding state and accessibility of antigen's idiotope to antibody are determining factors for affinity, specificity and valency with respect to antibody-antigen interaction. Claim 15 recites a substantially purified

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protein comprising an oligopeptide comprising at least 6 amino acid residues of the protein SEQ ID NO: 6, 7 or 8 and immunogenic fragments thereof. The specification provides insufficient guidance as to (i) "conservative motif(s)" of the protein for biological recognition and (ii) applicability of fully folded, or partially folded, or unfolded protein or oligopeptide to be used as a pharmaceutical composition. Since the claimed protein and peptide fragments are so structurally variant that they are functionally divergent in respect to their use in screening ligands and diagnosing and treating disorders associated with toxic compounds e.g. benzo(a)pyrene etc., the specification needs to provide sufficient guidance to support enabling.

On the other aspect, pollutant PAH compound not only induces multiple polynucleotide expression (see the foregoing statement) but also exerts its cellular pharmacological effect through aryl hydrocarbon receptor/transcription factor (AhR) and induces apoptosis (see Shafat, A. et al. (2000) Mol. Pharmacology. 58, 515-525). Thus, these cellular characteristics of PHA would have an unpredictable impact on the outcome of tissue expression profile as set forth in Table. The specification needs also to provide sufficient guidance or direction to support enabling.

(3) The quantity of experimentation necessary:

In the absence of working examples as to the unpredictable variants as stated above, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. The skilled artisan would be required to carry out an undue volume of search for appropriate protein(s) or peptide(s) in order for screening molecules in libraries (see page 23, the second paragraph). The number of the variants is at least  $1.7 \times 10^5$ . Considering a routine library of biomolecules is about  $10^7$ - $10^8$  (Clackson, T.

et al. *Trends in Biotechnol.* (1994) 12, 173-184), a combinational number calculated from  $1.7 \times 10^5 \times 10^8 = 1.7 \times 10^{13}$  represents the number required for each one of the protein and peptide variants to be tested. Owing to the peptide/protein variants being used as probes for screening a library is highly variant, the outcome of the screening would be highly unpredictable and representative of undue experimentation.

(4) The unpredictability of the art: applicable

Because of the claimed composition is a genus encompassing diverse peptide and protein variants of SEQ ID NO: 6, and uncertainty of choosing an appropriate pharmaceutical, the invention is unpredictable in the absence of factual indicia to the contrary (see the foregoing statement).

In addition, Applicants state that "an agonist of the polypeptide e.g. SEQ ID NO:6 may be administered to a subject to treat or prevent a disease associated with decreased expression or activity of the polypeptide" (see page 17, the fourth paragraph). However, there are no any examples provided in regard to this aspect. Thus, the proposed functions of the polypeptide by applicants are unpredictable as to whether the "agonist" of the protein is applicable to all asserted treatments as stated in the foregoing and what the positive or negative effect(s) would be. Until some actual and specific significance can be attributed to the protein identified in the specification as the polypeptide SEQ ID NO: 6 or/and agonist of the protein, one of ordinary skill in the art would have been required to performed additional or/and undue experimentation in order to determine how to use the claimed invention. Thus, the claims are not fully enable for all variants, fragments, immunogenic fragments as presently claimed.

(5) The relative skill of those in the art:

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The general knowledge and level of skill in the art do not supplement the omitted description with respect to an unpredictable number of the claimed oligopeptide, protein and immunogenic fragment variants. In view of the preceding factors (1-4), the level of skill in this art is high and requires at least a protein-engineer, an toxicologist and a cell biologist at Ph.D. level with several years of experience in peptide chemistry as well as knowledge in environmental chemistry, oncology and molecular biology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is unclear as to "a portion thereof" (item (a)); what does the "portion" refer to in term of the specific residues? does the portion contain only one amino acid residue? or is a portion of SEQ ID NO: 6 a full length of the polypeptide in which N-terminal  $\alpha$ -amino group has been deaminated or/and C-terminal carboxyl group has been decarboxylated? The specification also dose not appear to define what one skilled in the art would have been apprised of as to the variants and/or fragments. Dependent claims are also rejected.

***Claim Rejections - 35 USC § 102***

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Kikuno, R. et al (*DNA Res.* (1999) 6, 197-205).

Kikuno et al disclosed a polypeptide which is encoded by a cDNA clone (Accession number: AB029032) of ORF length 1,957 amino acids (see page 199, Table 1). The N-terminal portion of the disclosed polypeptide sequence (amino acid number 1371 to amino acid number 1957) is 100% identical to the SEQ ID NO: 6 of the instant application and encompasses at least an oligopeptide and an immunogenic fragment ( $\geq 5$  amino acids) of SEQ ID NO:6 which are recited by Claim 15 and 16 of the instant application absent factual data to the contrary. The alignment attached to the reference shows the amino acid sequence and would have been a substantially purified protein. Thus, Claims 15 and 16 are anticipated by the prior art of Kikuno et al.

### ***Claim Rejections - 35 USC §103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 15, 16 and 19 are rejected under 35 U.S.C. 103(a) as being obvious over Kikuno et al. (*DNA Res.* (1999) 6, 197-205) and Cunningham, M. J. et al (US Pat. NO: 6372431).

Kikuno et al. teach a polypeptide composition comprising a protein of SEQ ID NO: 6, as applied to Claims 15 and 16 of the instant application. However, Kikuno et al. do not teach a composition comprising a protein of SEQ ID NO:6 and a pharmaceutical carrier (e.g. a biochemical solution etc.).

Cunningham et al. teach a pharmaceutical comprising a substantially purified mammalian proteins, which are used in diagnostic and therapeutic applications including detecting toxicological response (e.g. response to PHA compound benzo(a)pyrene), in conjunction with a pharmaceutical carrier (see column 1, line 24, columns 2-3 [especially column 2, lines 9-14], column 4, lines 52-60, column 5, lines 15-20, and Claims 1 and 4), as applied to the limitation "a pharmaceutical carrier" of Claim 19 of the instant application. This would at least offer an advantage that the protein molecules can be used in a pharmaceutical composition in conjunction

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with a pharmaceutical carrier for the purpose of screening compounds and therapeutics for metabolic response indicative of toxic molecules.

Given the above motivation one of ordinary skill in the art would have combined the teachings of Kikuno et al and Cunningham et al. with respect to producing a composition comprising a protein of SEQ ID NO:6 and a pharmaceutical carrier for screening and diagnosing disorders associated with polycyclic aromatic hydrocarbon (PAH) exposure.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

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August 11, 2002

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